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Noninvasive Assessment of Subclinical Atherosclerosis using Flow-mediated Dilatation in Obese and Non-obese premenopausal women with Type 2 Diabetes Mellitus

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Abstract

Background: *Diabetes is well associated with atherosclerosis and patients have increased risk of cardiovascular events. Flow-mediated dilation study with ultrasonography on the brachial artery is a noninvasive method to estimate endothelial dysfunction, which is considered a marker of subclinical atherosclerosis. We conducted this study on premenopausal Diabetic women considering that the disease removes the protection to cardiovascular events conferred by sex and to detect the atherosclerosis at the subclinical stage where primary prevention may still be possible.*

Method: *A cross-sectional study in 101 premenopausal T2DM patients in the department of Medicine in collaboration with Radiodiagnosis department at Regional Institute of Medical Sciences. Patients were divided into 2 groups based on their BMI. They were subjected to ultrasonography on their brachial artery for FMD measurements.*

Result: *The mean age of the study patients was 41.11±2.47 years. The obese and non obese groups were compared for their FMD findings with the variables of age, blood glucose levels and duration of diabetes. Statistical significance was seen with all blood glucose level (fasting, postprandial and HbA1c) and also with the duration of diabetes but not with the age of the patients.*

Conclusion: *There was a positive correlation between endothelial dysfunction and duration of diabetes. Endothelial dysfunction as measured noninvasively by FMD of brachial artery can be useful tool for the detection of atherosclerosis at a subclinical stage.*

Key word: *Subclinical atherosclerosis, flow-mediated dilatation, premenopausal women, type 2 diabetes mellitus*

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I. INTRODUCTION

Diabetes mellitus (DM) is associated with aggressive vascular abnormalities and is regarded as the leading cause of morbidity and mortality.[1] Women usually are at a much lower cardiovascular risk than men but diabetes "erases" this female advantage.[2] Overall, diabetics are at a 2 to 4 fold increased risk of cardiovascular events relative to those without accounting for up to 80% of premature excess mortality. Obesity and excessive weight are able to change the vascular endothelium function. There is growing recognition that obesity is characterized by a low degree of chronic and subclinical inflammation.[3] So, when endothelial cells are exposed to risk factors such as insulin resistance and obesity, they are stimulated to express adhesion molecules on their surface, recruit several classes of leukocytes and promote the initial signaling mechanisms for cellular changes and atheroma formation. [4]

Studies have shown that when endothelial dysfunction exists, it is not limited to areas of atherosclerosis so that dysfunction in the brachial artery indicates dysfunction throughout the vascular system, including the

coronary arteries. [3] When systemic involvement of endothelial dysfunction is taken into consideration, checking from the peripheral arteries with noninvasive methods gives correct information.

In recent times, certain surrogate markers of atherosclerosis have help to assess the cardiovascular risk noninvasively.[5] Currently, endothelial dysfunction can be detected using simple, inexpensive, and noninterventional methods. Accessible localization of the brachial artery is ideal for evaluation of endothelial dysfunction noninvasively by Flow-mediated dilation method (FMD) using ultrasonography to measure brachial artery diameter before and after distal tissue ischemia.[6]

II. MATERIALS AND METHODS

This was a cross-sectional study in 101 T2DM patients who attended Medicine outpatients department and endocrine clinic and admitted in Medicine wards in collaboration with Radiodiagnosis department at Regional Institute of Medical Sciences (RIMS), Imphal. It was conducted for a period of two years from September 2017 to August 2019. Both newly diagnosed and known cases of premenopausal T2DM patients were included. The subjects were divided into 2 groups, obese (51 patients)and non obese (50 patients). After obtaining an informed consent, detailed clinical history including patient particulars were taken.

Measurement of Endothelium-dependent FMD.

They were made to fast for at least 8 to 12 h before the study and all possible confounding factors were avoided in preparation for the study.

A sphygmomanometric cuff was placed above the antecubital fossa and baseline rest image was acquired then blood flow was estimated by time-averaging the pulsed Doppler velocity signal obtained .Thereafter, arterial occlusion was created by cuff inflation to suprasystolic pressure of atleast 50 mm Hg above systolic pressure for 2 minutes.This caused ischemia and consequent dilation of downstream resistance vessels via autoregulatory mechanisms. Subsequent cuff deflation induced a brief high-flow state through the brachial artery to accommodate the dilated resistance vessels. The resulting increase in shear stress caused the brachial artery to dilate. The longitudinal image of the artery was recorded immediately after cuff release and at 1 minute after cuff deflation. The change in the diameter of brachial artery was calculated as-

FMD = (d2 – d1) x 100 / d1

d1 - brachial artery diameter at baseline

d2– diameter of brachial artery at 1 minute after cuff release.

Endothelial dysfunction is considered present if calculated FMD is <4.5%.

Statistical analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD and results on categorical measurements are presented in Number (%). p value of <0.05 was considered statistically significant. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Ethical approval: Ethical approval was obtained from the Research Ethics Board, RIMS.

III. RESULTS AND OBSERVATION

The mean age of the patients in the study was 41.11 years with a standard deviation of 2.47 years .They were grouped on the basis of their BMI as obese 51(50.5%) and non obese 50 (49.5%). Amongst the 50 non obese patients, 34(68%) patients were overweight while 16(32%) patients had normal weight. The blood glucose values between the two groups was comparable with mean FBS (mg/dl) being 124.04±21.25 in the non-obese group and 127.76±33.063 in the obese group, and mean PPBS (mg/dl) being 168.68±44.156 and 164.47±44.27 respectively in the non-obese and obese group.

Most of the patients 90(89.1%) patients were on oral hypoglycemic agents (OHA) and only 11(10.9%) patients were on insulin therapy. In the obese group, 43(84.3%) patients were on OHA and 8(15.7%) were on insulin therapy while in the non obese group, 47(94%) was on OHA and 3(6%) were on insulin therapy. There was no patient on both OHA and insulin therapy.

Table 1: Distribution of patients by age and BMI.

	BMI		
Age in years	**18.5 - 22.9**	**23 - 24.9**	≥25
31 - 35	0 (0%)	2(5.9%)	1(2%)
36 - 40	7(43.8%)	13(38.2%)	12(23.5%)

41 - 44	9(56.3%)	19(55.9%)	38(74.5%)
Total	16(100%)	34(100%)	51(100%)

Table 2: Distribution of patients by FBS, PPBS and HbA1c in groups.

variables	**BMI** <18.5 (n=0)	18.5-22.9 (n=16)	23-24.9 (n=34)	≥25 (n=51
FBS (mg/dl)				
<100	0(0%)	2(12.5%)	3(8.8%)	6(11.8%)
100-126	0(0%)	10(16.5%)	20(58.8%)	29(56.9%)
>126	0(0%)	4(25%)	11(32.4%)	16(31.4%)
PPBS (mg/dl)				
<140	0(0%)	6(37.5%)	8(23.5%)	15(29.4%)
140 - 200	0(0%)	6(37.5%)	18(52.9%)	27(52.9%)
> 200	0(0%)	4(25%)	8(23.5%)	9(17.6%)
HbA1c%				
<7	0(0%)	6(37.5%)	12(35.3%)	20(39.2%)
7 - 9	0(0%)	10(62.5%)	22(64.7%)	30(58.8%)
> 9	0(0%)	0(0%)	0(0%)	1(2%)

Table 3: Distribution of family history in relation to BMI of study patients.

Family history	**Non obese**	**Obese**
Yes	7(36.8%)	12(63.2%)
No	43(52.4%)	39(47.6%)
Total	50(49.5%)	51(50.5%)

Table 4: Distribution of antidiabetic medications in non-obese and obese

Diabetic medication	**Non obese**	**Obese**
OHA	47(94%)	43(84.3%)
Insulin	3(6%)	8(15.7%)
Total	50	51

Table 6: Distribution of patients by FMD in non-obese and obese

FMD	**Non obese**	**Obese**
<4.5	4(8%)	13(25.5%)
4.5 - 7.9	9(18%)	2(3.9%)
8- 11.9	21(41%)	15(29.4%)
≥12	16(32%)	21(41.2%)
Total	50	51

Table 7: Distribution of patients by duration of diabetes in patients with abnormal and normal FMD

Duration of Diabetes in years	**Abnormal FMD**	**Normal FMD**
<1	2(11.8%)	3(3.6%)
1 - 2	3(17.6%)	54(64.3%)
3 - 5	1(5.9%)	25(29.8%)
6 - 9	11(64.7%)	2(2.4%)
Total	17	84

Table 8: Comparison of variables according to FMD of the study patients .

Variables	**FMD**				**Mean ±SD**	**p value**
	<4.5	**4.5 - 7.9**	**8 - 11.9**	≥12		
Age in years	42.67±1.37	40.50±2.38	40.76±2.80	41.19±2.26	41.11±2.47	0.09
FBS (mg/dl)	151.25±28.71	145±43.78	123.39±22.86	113.08±11.42	125.92±27.78	<0.001
PPBS (mg/dl)	213.33±42.68	194.71±62.63	163.13±39.35	144.24±16.20	166.55±44.05	<0.001
HbA1c%	8.17±0.83	7.79±1.25	6.99±0.83	6.35±0.54	7.01±1.02	<0.001
Diabetes duration in years	5.83±2.79	2.79±2.15	2.47±1.41	1.78±1.18	2.66±2.05	<0.001

IV. DISCUSSION

Atherosclerosis which is accelerated in diabetic patients , is the leading cause of morbidity and mortality .The subclinical process precedes clinical manifestation by years and so when clinical findings appear, involvement is usually advanced and intervention thereafter are palliative or aimed at secondary prevention. It is therefore important to intervene in the vascular alteration at a far earlier stage to prevent, from the very beginning the development of atherosclerosis and the resulting complications on the target organ level.[7] As endothelial cell dysfunction occurs very early in the disease process, assessment of endothelial function, thus, can be used an early marker of future atherosclerotic disease.

The study included 101 patients of T2DM aged 31 to 44 years grouped as obese and non obese. The most common age bracket was 41 to 44 years comprising 65.34% similar to a study by Nakhjavani et al.[8] There

was 19 patients with positive family history of DM with distribution across groups as 12(23.5%), 7(14%) in the obese and non obese group. This has near comparison with a similar study by Bhargava K et al.[9]

In our study, endothelial dysfunction expressed as FMD% < 4.5 was present in 17 of 101 patients . Amongst them 13 patients were obese and 4 patients non-obese. These patients with endothelial dysfunction had longer duration of diabetes compared to those without; 11(64.7%) patients have had diabetes for 6-9 years with the mean duration of diabetes being 5.83±2.79 years. There was endothelial dysfunction also seen in 2 newly diagnosed T2DM in our study, which is probably due to late detection of the disease.

Those with endothelial dysfunction had higher blood sugar values (mean FBS and PPBS in mg/dl was 151.25±28.71 and 213.33±42.68). Mean HbA1c(%) levels in them was also higher at 8.17±0.83 which is comparable to the study by Chugh SN et al[10] which reported mean HbA1c of 8.45±0.30. The findings of present study is also consistent with that of Kawano et al.[11] In their study on endothelial dysfunction, it was seen that hyperglycaemia in response to oral glucose loading rapidly suppressed endothelium dependent vasodilation, probably through increased production of oxygen-derived free radicals ,strongly suggesting that prolonged and repeated post-prandial hyperglycemia could play an important role in the development and progression of atherosclerosis.

On the other hand ,subjects with good endothelial function(FMD≥12) had better blood glucose control with mean FBS and PPBS being 113.08±11.42 mg/dl and 144.24±16.20 respectively and mean HbA1c being 6.35±0.54. The findings were again consistent with Chugh SN et al[10] study where FMD% of 11.94±3.33% was observed with better glycemic control. These patients also had shorter duration of diabetes of 1.78±1.18 years.

In the comparison of patients with endothelial dysfunction defined by FMD < 4.5 against patients with normal endothelial function with the variables of age, blood glucose levels and duration of diabetes. Except for the patient‘s age (p value of .09) there was statistical significance (p value < .001) seen for the various blood glucose levels (fasting, postprandial and HbA1c) and duration of Diabetes Mellitus. Such similar findings were reported by Satpathy et al[12] on their study on endothelial dysfunction in patients of DM. They saw a significant inverse relation between DM duration and endothelial dysfunction and also found an inverse relation between HbA1C and endothelial dysfunction .

V. CONCLUSION

There was a positive correlation between endothelial dysfunction with the blood glucose levels and duration of diabetes in premenopausal T2 DM patients. Endothelial dysfunction as measured noninvasively by FMD of brachial artery can be useful tool for the detection of atherosclerosis at a subclinical stage with the possibility of primary prevention for cardiovascular diseases.

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